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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,263	09/28/2005	Toshihiro Nakashima	NAKASHIMA6	3356

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EXAMINER	
OGUNBIYI, OLUWATOSIN A	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,263	NAKASHIMA ET AL.	
	Examiner	Art Unit	
	Oluwatosin Ogunbiyi	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 9/18/05 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 9/18/2006.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendments to the claims filed 9/28/05 have been entered into the record. Claims 1-20 are now pending.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Drawings

The drawings in this application have been accepted. No further action by Applicant is required.

Information Disclosure Statement

The information disclosure statement filed 9/18/06 has been considered. An initialed copy is enclosed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2,3,8,9-13,18-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,4,6-9 of copending Application No.10/570,499. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant claims are drawn to a modified Staphylococcal enterotoxin B (SEB) having a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) wherein the reactivity with the anti-SEB antibody was reduced by introducing arbitrary amino acid substitution in the amino acid sequence of SEB at an epitope recognition site of the anti-SEB antibody in the amino acid sequence of SEB wherein Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr.

The claims of the 10/570,499 application are drawn to a modified Staphylococcal enterotoxin B (SEB) having an amino acid substitution to allow for resistance to a protease, or derivative thereof, wherein in the modified SEB or derivative thereof has an amino acid sequence as set forth in SEQ ID NO: 1 wherein asparagine at 23 position is substituted with tyrosine.

The 10/570, 499 ('499) claims teach the instant modified SEB wherein asparagine at 23 position is substituted with tyrosine. Thus, the SEB of the '499

application also possess the functionally inherent properties as recited in claim 1 of the instant application (i.e. reduced reactivity with a neutralizing antibody). Both applications claim the same modified SEB product and the limitations such as 'a prophylactic/remedy for immunopathy (rheumatoid arthritis) in a form for oral administration' recited in the instant application and ' vaccine or to allow for resistance to a protease' recited in the '499 are all intended uses of the product and bear no patentable weight on the product. The instant application and the '499 application both claim the same product i.e. a modified SEB wherein asparagine at 23 position is substituted with tyrosine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-11 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a remedy for rheumatoid arthritis does not reasonably provide enablement for a prophylactic for rheumatoid arthritis or a prophylactic/remedy for immunopathy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are also drawn to a prophylactic/remedy adapted for immunopathy comprising as an active ingredient the modified SEB as set forth in claim 1 wherein said prophylactic/remedy has a reduced immunological response to SEB and an inhibitory activity to T cell activation wherein said immunopathy is rheumatoid arthritis.

The nature of the instant invention is the use of a modified Staphylococcus Enterotoxin B (SEB) to prevent (prophylaxis) immunopathy. Said immunopathy can be rheumatoid arthritis.

The instant specification does not define immunopathy and the term is not a term that is normally used in the art.

The teachings of the specification are limited to inhibition of symptoms of arthritis by administering a modified SEB (p. 27 lines 4-7). The specification does not provide guidance on how to prevent rheumatoid arthritis with the instantly claimed modified SEB.

The art as at the time of filing teaches that "until we know the exact cause of rheumatoid arthritis and can therefore direct therapy at the inciting cause or at the earliest steps in the pathophysiologic sequence, the molecules mediating joint damage are the logical targets of anti-rheumatoid arthritis therapy" (Smith et al. Ann Intern Med 2002; 136:908-922 p. 916 right column last paragraph to p. 917). Thus, there is no preventative therapy for rheumatoid arthritis.

The instant specification has not elucidated the cause of rheumatoid arthritis and it is therefore unpredictable that the instantly claimed modified SEB can prevent rheumatoid arthritis and there is no working example in the specification where rheumatoid arthritis has been prevented. The specification only teaches inhibition of symptoms in mice already having arthritis. The specification also does not define immunopathy and does not provide a working example as to the prevention of other types of immunopathy or inhibition of symptoms of other types of immunopathy.

In view of the above considerations particularly the guidance in the specification and the teachings in the art, the instant specification has not enabled the full scope of the claims and one of skill in the art would not know how to use the invention as claimed as a prophylactic for rheumatoid arthritis or a prophylactic or remedy for other immunopathy without undue experimentation.

Claims 3, 9-11,13 and 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-11 and 18-20 are drawn to a prophylactic/remedy adapted for immunopathy comprising as an active ingredient the modified SEB as set forth in claim 1 or claim 8, wherein said prophylactic/remedy has a reduced immunological response to SEB and an inhibitory activity to T cell activation.

The claim is confusing as written. How can the active ingredient i.e. a modified SEB have a reduced immunological response to SEB? Appropriate clarification of the claims is requested.

As to claim 3, the claim recites "the modified SEB of claim 2 wherein the amino acid substitution was introduced at an epitope recognition site of the anti-SEB antibody in the amino acid sequence of SEB" As written, the claim is confusing because it is not

clear whether the amino acid substitution is introduced into the anti-SEB antibody or into the amino acid sequence of SEB.

As to the term 'immunopathy', the term is not a term of art and the specification does not define the term. Thus, the metes and bounds of immunopathy is not clear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 8-13 and 18-20 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sasaki et al. EP 1055429 A1 published 11/29/2000.

The claims are drawn to a modified Staphylococcal enterotoxin B (SEB) having a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) wherein the reactivity with the anti-SEB antibody was reduced by introducing arbitrary amino acid substitution in the amino acid sequence of SEB wherein the amino acid substitution was introduced at an epitope recognition site of the anti-SEB antibody in the amino acid sequence of SEB wherein Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr. The claims are also drawn to a prophylactic/remedy adapted for immunopathy comprising as an active ingredient the modified SEB as set forth in claim

1 or claim 8, wherein said prophylactic/remedy has a reduced immunological response to SEB and an inhibitory activity to T cell activation.

Sasaki et al teaches a modified Staphylococcal enterotoxn B (SEB). Sasaki teaches said modified enterotoxin with arbitrary amino acid substitutions at epitope recognition site (p.3 paragraph 12 -14, p. 4 paragraphs 17, 18, 19, 23, p. 8 table 3). Sasaki teaches a modified SEB wherein Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr (p.3 paragraph 12, p. 8 table 3). Since Sasaki discloses a modified SEB as instantly claimed, for example, Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr, said modified SEB of Sasaki et al inherently possess reduced reactivity with a neutralizing anti-SEB antibody and possesses reduced immunological response to SEB and an inhibitory activity to T cell activation. Recitation of 'prophylactic/remedy adapted for immunopathy' is an intended use and does not structurally distinguish the claimed product from the product of the prior art and therefore is not given patentable weight for the claimed product. In the instant case, the art disclosed identical product with identical structure as instantly claimed and any function(s) of said product is inherent to said structure.

Nevertheless, Sasaki teaches that said modified enterotoxin is used as a prophylactic/remedy for immunopathy (e.g. rheumatoid arthritis) having reduced immunological response to SEB and inhibitory activity on T cell activation (see abstract and claims 1-13 p. 12) and is in a form for oral administration (claims 1-13).

Claims 1-4 and 9-11 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Nishi et al. The Journal of Immunology, 1997, 1558:247-254.

The claims are drawn to a modified Staphylococcal enterotoxin B (SEB) having a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) wherein the reactivity with the anti-SEB antibody was reduced by introducing arbitrary amino acid substitution in the amino acid sequence of SEB wherein the amino acid substitution was introduced at an epitope recognition site of the anti-SEB antibody in the amino acid

sequence of SEB wherein the amino acid substitution was introduced within a region from Lys at 226-position to Lys at 229-position in the amino acid sequence of SEB. The claims are also drawn to a prophylactic/remedy adapted for immunopathy comprising as an active ingredient the modified SEB as set forth in claim 1.

Nishi et al teaches a modified Staphylococcal enterotoxn B (SEB). Nishi teaches said modified enterotoxin with arbitrary amino acid substitutions at an epitope recognition site (p.250 column 1 last bridging paragraph to column 2). Nishi teaches a modified SEB wherein the amino acid substitution was introduced within a region from Lys at 226-position to Lys at 229-position in the amino acid sequence of SEB (p.250 column 1 last bridging paragraph to column 2). Nishi teaches that said modified enterotoxin has reduced reactivity with an IgG antibody (p. 252 fig. 6 and column 2 last two paragraphs to p. 253 first paragraph). Since Nishi discloses a modified SEB as instantly claimed, for example, with an amino acid substitution introduced within a region from Lys at 226-position to Lys at 229-position in the amino acid sequence of SEB, said modified SEB of Nishi et al inherently possess reduced reactivity with a neutralizing anti-SEB antibody and possesses reduced immunological response to SEB and an inhibitory activity to T cell activation. Nishi teaches said modified SEB is purified and dialyzed against PBS (phosphate buffered saline). Thus, said modified SEB is in a form for oral administration as PBS is a pharmaceutically acceptable carrier.

Recitation of 'prophylactic/remedy adapted for immunopathy' is an intended use and does not structurally distinguish the claimed product from the product of the prior art and therefore is not given patentable weight for the claimed product. In the instant case, the art disclosed identical product with identical structure as instantly claimed and any function(s) of said product is inherent to said structure.

Claims 1-3, 8-13 and 18-20 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kappler et al. WO93/14634 Aug. 5 1993. The claims are set forth supra.

Kappler et al teaches a modified Staphylococcal enterotoxn B (SEB) (p. 38). Kappler teaches said modified enterotoxin with arbitrary amino acid substitutions at epitope recognition site (p.38 table II). Kappler teaches a modified SEB wherein Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr (p.38 table II and III see BC-66 mutant). Since Kappler et al discloses a modified SEB as instantly claimed, for example, Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr, said modified SEB of Kappler et al inherently possess reduced reactivity with a neutralizing anti-SEB antibody and possesses reduced immunological response to SEB and an inhibitory activity to T cell activation. Kappler et al teaches said modified SEB in a balanced salt solution (BSS) thus said modified SEB is in a form for oral administration.

Recitation of 'prophylactic/remedy adapted for immunopathy' is an intended use and does not structurally distinguish the claimed product from the product of the prior art and therefore is not given patentable weight for the claimed product. In the instant case, the art disclosed identical product with identical structure as instantly claimed and any function(s) of said product is inherent to said structure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being obvious over Nishi et al. The Journal of Immunology, 1997, 1558:247-254 in view of Sasaki et al EP 1055429 A1 published 11/29/2000 and Kappler et al. WO93/14634 Aug. 5 1993.

The claims are drawn to a modified Staphylococcal enterotoxin B (SEB) having a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) wherein the reactivity with the anti-SEB antibody was reduced by introducing arbitrary amino acid substitution in the amino acid sequence of SEB wherein the amino acid substitution was introduced at an epitope recognition site of the anti-SEB antibody in the amino acid sequence of SEB wherein the amino acid substitution was introduced within a region from Lys at 226-position to Lys at 229-position in the amino acid sequence of SEB. The claims are also drawn to a prophylactic/remedy adapted for immunopathy comprising as an active ingredient the modified SEB as set forth in claim 1.

Nishi et al teaches a modified Staphylococcal enterotoxn B (SEB). Nishi teaches said modified enterotoxin with arbitrary amino acid substitutions at an epitope recognition site (p.250 column 1 last bridging paragraph to column 2). Nishi teaches a

modified SEB wherein the amino acid substitution was introduced within a region from Lys at 226-position to Lys at 229-position in the amino acid sequence of SEB (p.250 column 1 last bridging paragraph to column 2). Nishi teaches that said modified enterotoxin has reduced reactivity with an IgG antibody (p. 252 fig. 6 and column 2 last two paragraphs to p. 253 first paragraph). Since Nishi discloses a modified SEB as instantly claimed, for example, with an amino acid substitution introduced within a region from Lys at 226-position to Lys at 229-position in the amino acid sequence of SEB, said modified SEB of Nishi et al inherently possess reduced reactivity with a neutralizing anti-SEB antibody and possesses reduced immunological response to SEB and an inhibitory activity to T cell activation. As to the 'recitations of a prophylactic/remedy adapted for immunopathy... for oral administration' said limitations are intended uses of the instantly claimed modified SEB and bear no patentable weight.

Nishi does not teach said modified SEB with the amino acid sequence from 226-229 of SEB is Leu Phe Ala Ala or Ala Thr Thr Gln or Lys Arg Ile Ile and does not teach said modified SEB wherein Asn at 23 position in the amino acid sequence of said modified SEB is substituted with Tyr.

Sasaki teaches a modified SEB wherein Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr (p.3 paragraph 12, p. 8 table 3). Sasaki teaches that said modified SEB is used for a remedy for immunopathy such as rheumatoid arthritis because said amino acid substitution at position 23 results in a SEB that has inhibitory activity on T cell activation with reduced toxicity (see abstract and p. 3 paragraph 9, 10, 21). Sasaki also teaches how to introduce amino acid substitutions into SEB.

Kappler teaches a modified SEB wherein Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr (p.38 table II and III see BC-66 mutant). Kappler et al teaches the benefits of introducing a mutation at amino acid positions 23 of SEB (and other amino acid positions) i.e. the elicitation of protective immune response (e.g. antibody production) without inducing T cell proliferation i.e. without inducing pathological effects of said SEB superantigen (see abstract, p. 1 lines 1-15, p.

9 lines 10-36 to p. 10 lines 1-22). Kappler also teaches methods for introducing random or arbitrary mutations in SEB (p. 23 example 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to introduce other amino acid substitutions in position 226-229 of the SEB of Nishi et al as taught by Sasaki et al and Kappler et al who teach methods for introducing random mutations in SEB because Nishi teaches that amino acid residues 226-229 of SEB are recognized by antibody to SEB and that amino acid substitutions in position 226-229 results in a SEB with reduced activity to a SEB antibody. Thus, giving the teachings of Nishi, one of ordinary skill in the art can try different combinations of amino acid substitutions in position 226-229 (epitope recognition site) using methods known in the art for introducing random or arbitrary substitutions into SEB (as taught by Sasaki et al and Kappler et al) to arrive at a modified SEB with reduced reactivity with SEB neutralizing antibody with a reasonable expectation of success.

It would also have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to additionally introduce an amino acid substitution at residue 23 i.e. replacing Asn with Tyr in the modified SEB of Nishi et al because Sasaki and Kappler et al teach that such an amino acid substitution results in a SEB superantigen that is less toxic without introduction of the pathological effects of said superantigen. For the same reasons, one of skill in the art would also substitute Asn for Tyr in other modified SEBs having different combinations of amino acid substitutions in position 226-229 as set forth supra.

Status of the Claims

Claims 1-20 are rejected. No claims allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-0855. The examiner can normally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Examiner Shanon Foley can be reached on 571-272-0898.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Oluwatosin Ogunbiyi
Examiner
Art Unit 1645

PATRICIA A. DUFFY
PRIMARY EXAMINER